

We claim:

1. A method for inducing arteriogenesis, lymphangiogenesis, vasculogenesis, or cardiomyogenesis, comprising administering to a cell or tissue in need thereof a dose of a polynucleotide that encodes a vascular endothelial growth factor (VEGF), or that
5 encodes a polypeptide comprising an active site of the VEGF, wherein the coding sequence is operably linked to an expression control sequence, the dose being sufficient to induce arteriogenesis, lymphangiogenesis, vasculogenesis, or cardiomyogenesis.

2. The method of claim 1, wherein the VEGF is VEGF1-165, whose amino acid
10 sequence is:

	Ala	Pro	Met	Ala	Glu	Gly	Gly	Gly	Gln	Asn
	His	His	Glu	Val	Val	Lys	Phe	Met	Asp	Val
	Tyr	Gln	Arg	Ser	Tyr	Cys	His	Pro	Ile	Glu
	Thr	Leu	Val	Asp	Ile	Phe	Gln	Glu	Tyr	Pro
15	Asp	Glu	Ile	Glu	Tyr	Ile	Phe	Lys	Pro	Ser
	Cys	Val	Pro	Leu	Met	Arg	Cys	Gly	Gly	Cys
	Cys	Asn	Asp	Glu	Gly	Leu	Glu	Cys	Val	Pro
	Thr	Glu	Glu	Ser	Asn	Ile	Thr	Met	Gln	Ile
	Met	Arg	Ile	Lys	Pro	His	Gln	Gly	Gln	His
20	Ile	Gly	Glu	Met	Ser	Phe	Leu	Gln	His	Asn
	Lys	Cys	Glu	Cys	Arg	Pro	Lys	Lys	Asp	Arg
	Ala	Arg	Gln	Glu	Asn	Pro	Cys	Gly	Pro	Cys
	Ser	Glu	Arg	Arg	Lys	His	Leu	Phe	Val	Gln
	Asp	Pro	Gln	Thr	Cys	Lys	Cys	Ser	Cys	Lys
25	Asn	Thr	Asp	Ser	Arg	Cys	Lys	Ala	Arg	Gln
	Leu	Glu	Leu	Asn	Glu	Arg	Thr	Cys	Arg	Cys
	Asp	Lys	Pro	Arg	Arg	(SEQ ID NO: 1).				

3. The method of claim 1, wherein arteriogenesis is induced.

4. The method of claim 1, wherein cardiomyogenesis is induced.

30 5. The method of claim 3, wherein the arteriogenesis is induced *in vitro*, *in vivo*, or *ex vivo*.

6. The method of claim 3, wherein the induced arteriogenesis is localized.

7. The method of claim 3, wherein the arteriogenesis is induced in normoperfused tissue, *in vitro*, *in vivo*, or *ex vivo*.

8. The method of claim 3, wherein the arteriogenesis is induced in ischemic tissue, *in vitro*, *in vivo*, or *ex vivo*.
9. The method of claim 3, wherein the arteriogenesis is induced in myocardial tissue, *in vitro*, *in vivo*, or *ex vivo*.
- 5 10. The method of claim 4, wherein the cardiomyogenesis is induced *in vitro*, *in vivo*, or *ex vivo*.
11. The method of claim 4, wherein the induced cardiomyogenesis is localized.
12. The method of claim 4, wherein the cardiomyogenesis is induced in normoperfused tissue, *in vitro*, *in vivo*, or *ex vivo*.
- 10 13. The method of claim 4, wherein the cardiomyogenesis is induced in ischemic tissue, *in vitro*, *in vivo*, or *ex vivo*.
14. The method of claim 4, wherein the cardiomyogenesis is induced in myocardial tissue, *in vitro*, *in vivo*, or *ex vivo*.
- 15 15. The method of claim 4, wherein the cardiomyogenesis is of striated, smooth, or myoepithelial cells.
16. The method of claim 15, wherein the striated cells include cardiomyocytes, skeletal cells, and/or skeletal myoblasts.
17. The method of claim 16, wherein the skeletal muscle cells include skeletal muscle type I and type II cells and skeletal myoblasts.
- 20 18. The method of claim 15, wherein the smooth muscle cells include vascular smooth muscle cells and/or non-vascular smooth muscle cells.
19. The method of claim 1, wherein the cell or tissue is eukaryotic.
20. The method of claim 1, wherein the cell or tissue is mammalian.
21. The method of claim 1, wherein the cell or tissue is porcine or human.
- 25 22. The method of claim 1, wherein the cell or tissue is human.
23. The method of claim 1, wherein the polynucleotide is a genomic DNA, a cDNA, or a messenger RNA.
24. The method of claim 23, wherein the polynucleotide encodes the polypeptide represented by SEQ ID NO: 1.
- 30 25. The method of claim 24, wherein the polynucleotide is a cDNA.
26. The method of claim 23, wherein the polynucleotide encodes a polypeptide comprising an active site of the polypeptide represented by SEQ ID NO: 1.
27. The method of claim 26, wherein the polynucleotide is a cDNA.
28. The method of claim 1, wherein the polynucleotide is inserted in a vector.

29. The method of claim 28, wherein the vector is a plasmid vector.
30. The method of claim 29, wherein the plasmid vector containing the polynucleotide is pUVEK15.
31. The method of claim 1, wherein the polynucleotide is administered to the cell or
5 tissue in a liposome.
32. The method of claim 28, wherein the polynucleotide inserted in a vector is administered to the cell or tissue in a liposome.
33. The method of claim 1, which is carried out in vivo, and wherein a sufficient dose of the polynucleotide is administered to a subject in need of such treatment to induce
10 arteriogenesis, lymphangiogenesis, vasculogenesis, or cardiomyogenesis.
34. The method of claim 33, wherein the subject exhibits signs or symptoms of, or suffers from, myocardial infarction, myocardial ischemia, dilated cardiomyopathy, or hypertrophic cardiomyopathy.
35. The method of claim 33, wherein the subject is a human patient.
- 15 36. The method of claim 33, wherein the polynucleotide is in the form of a pharmaceutical composition.
37. The method of claim 33, wherein the polynucleotide is administered by a parenteral, sublingual, inhalatory, oral or rectal route.
38. The method of claim 37, wherein the administration is parenteral, comprising
20 administering the polynucleotide in vehicles that are microbubbles, and then disrupting the microbubbles by ultrasound directed at a site of interest, such that the polynucleotide is released at and introduced into the site of interest.
39. The method of claim 37, wherein the administration is parenteral and is intravascular, intracelomic, intramuscular, subcutaneous, intraspinal, topical or
25 intracardiac administration.
40. The method of claim 39, wherein the administration is intravascular and is intravenous or intra-arterial administration.
41. The method of claim 40, wherein the administration is intra-arterial and is intracoronary, intra-aortic, intrafemoral, intrapopliteal, intrapedialis, intra-posterior
30 tibialis, intracarotideal or intraradialis administration.
42. The method of claim 39, wherein the administration is intracelomic and is intrapericardial, intraperitoneal, intra-amniotic sac or intrapleural administration.
43. The method of claim 39, wherein the administration is intramuscular and is intramyocardial or intra-peripheral muscle administration.

44. The method of claim 43, wherein the administration is intramyocardial and is transepical or transendocardial administration.
45. The method of claim 39, wherein the administration is topical and is periadventitial, perivascular, epicardial, epidermal, transdermal, ophthalmic or mucous absorption administration.
46. The method of claim 45, wherein the administration is by mucous absorption and is administration through a conjunctival, nasopharyngeal, bucopharyngeal, laryngopharyngeal, vaginal, colonic, urethral or vesicle mucosum.
47. The method of claim 46, wherein the administration is by absorption through the bucopharyngeal mucosum and is through a yugalis, gingivoyugalis or gingivolabialis mucosum.
48. The method of claim 39, wherein the administration is intracardiac and is intra-atrial or intraventricular administration.
49. The method of claim 48, wherein the administration is intra-atrial and is intra-left atria administration or intra-right atria administration.
50. The method of claim 48, wherein the administration is intraventricular and is intra-left ventricle administration or intra-right ventricle administration.
51. The method of claim 33, wherein the administration is intramyocardial-transepical injection under direct visualization, or intramyocardial-transendocardial injection under fluoroscopic guidance.
52. The method of claim 33, wherein the polynucleotide is administered by injection perpendicular to the plane of the area of injection.
53. The method of claim 33, wherein the polynucleotide is administered by injection parallel to the plane of the area of injection.
54. The method of claim 33, wherein the polynucleotide is administered by injection at an oblique angle in relation to the plane of the area of injection.
55. The method of claim 54, wherein the angle in relation to the plane of the area of injection is between about 30° and about 90°.
56. The method of claim 33, wherein the polynucleotide is administered by injections that are homogeneously or heterogeneously distributed in the area of injection.
57. The method of claim 33, wherein the polynucleotide sequence encodes VEGF1-165, whose amino acid sequence is represented by SEQ ID NO: 1.
58. The method of claim 33, wherein the polynucleotide sequence encodes an active site of the polypeptide represented by SEQ ID NO: 1.

59. The method of claim 33, wherein the polynucleotide is administered in a single dose of between about 0.003 and about 0.36 nmoles /kg, wherein the nmoles are of polynucleotide encoding an active VEGF polypeptide.

60. The method of claim 59, wherein the polynucleotide is administered in a single
5 dose of about between about 0.01 and about 0.10 nmoles/kg.

61. The method of claim 59, wherein the polynucleotide is administered in two or more doses, to achieve a total dose of between about 0.003 and about 0.36 nmoles /kg.

62. The method of claim 61, wherein the polynucleotide is administered in two or
10 more doses, to achieve a total dose of between about 0.01 and about 0.10 nmoles/kg.

63. The method of claim 33, wherein the polynucleotide is inserted in a plasmid vector and is pUVEK15VEGF.

64. The method of claim 63, wherein the concentration of the pUVEK15VEGF is between about 0.5 and about 4 mg/mL.

15 65. A method for inducing mitosis or proliferation of a smooth muscle cell, a skeletal muscle cell, or a cardiomyocyte, comprising administering to the cell a dose of a polynucleotide that encodes a vascular endothelial growth factor (VEGF), or that encodes a polypeptide comprising an active site of the VEGF, wherein the coding sequence is operably linked to an expression control sequence, the dose being
20 sufficient to induce the mitosis or proliferation.

66. The method of claim 65, wherein the VEGF is VEGF1-165, whose amino acid sequence is:

	Ala	Pro	Met	Ala	Glu	Gly	Gly	Gly	Gln	Asn
	His	His	Glu	Val	Val	Lys	Phe	Met	Asp	Val
25	Tyr	Gln	Arg	Ser	Tyr	Cys	His	Pro	Ile	Glu
	Thr	Leu	Val	Asp	Ile	Phe	Gln	Glu	Tyr	Pro
	Asp	Glu	Ile	Glu	Tyr	Ile	Phe	Lys	Pro	Ser
	Cys	Val	Pro	Leu	Met	Arg	Cys	Gly	Gly	Cys
	Cys	Asn	Asp	Glu	Gly	Leu	Glu	Cys	Val	Pro
30	Thr	Glu	Glu	Ser	Asn	Ile	Thr	Met	Gln	Ile
	Met	Arg	Ile	Lys	Pro	His	Gln	Gly	Gln	His
	Ile	Gly	Glu	Met	Ser	Phe	Leu	Gln	His	Asn
	Lys	Cys	Glu	Cys	Arg	Pro	Lys	Lys	Asp	Arg
	Ala	Arg	Gln	Glu	Asn	Pro	Cys	Gly	Pro	Cys

Ser	Glu	Arg	Arg	Lys	His	Leu	Phe	Val	Gln
Asp	Pro	Gln	Thr	Cys	Lys	Cys	Ser	Cys	Lys
Asn	Thr	Asp	Ser	Arg	Cys	Lys	Ala	Arg	Gln
Leu	Glu	Leu	Asn	Glu	Arg	Thr	Cys	Arg	Cys

5 Asp Lys Pro Arg Arg (SEQ ID NO: 1).

67. The method of claim 65, wherein the smooth muscle cell is in a myocardial tissue.
68. The method of claim 65, wherein the smooth muscle cell is in a skeletal tissue.
69. The method of claim 65, wherein the cardiomyocyte is in a cardiac tissue.
70. The method of claim 65, wherein the smooth muscle cell is in a muscle tissue.
- 10 71. The method of claim 65, wherein the mitosis or proliferation is induced in vitro, in vivo, or ex vivo.
72. The method of claim 65, wherein the cell or tissue is eukaryotic.
73. The method of claim 65, wherein the mitosis or proliferation is localized mitosis or proliferation.
- 15 74. The method of claim 65, wherein the mitosis or proliferation is induced in normoperfused tissue, in vivo, in vitro, or ex vivo.
75. The method of claim 65, wherein the mitosis or proliferation is induced in ischemic tissue, in vivo, in vitro, or ex vivo.
76. The method of claim 65, wherein the mitosis or proliferation induces tissue
- 20 regeneration, in vitro, in vivo, or ex vivo.
77. The method of claim 76, wherein the tissue is normoperfused tissue.
78. The method of claim 76, wherein the tissue is ischemic tissue.
79. The method of claim 76, wherein the tissue is myocardial tissue.
80. The method of claim 76, wherein the tissue is hypoperfused tissue.
- 25 81. A kit comprising
 - (a) a polynucleotide that encodes a vascular endothelial growth factor (VEGF), or that encodes a polypeptide comprising an active site of the VEGF, wherein the coding sequence is operably linked to an expression control sequence, and
 - (b) a label or instructions indicating a use for the polynucleotide to induce
- 30 arteriogenesis, lymphangiogenesis, vasculogenesis, cardiomyogenesis, or mitosis or proliferation of a smooth muscle cell, a skeletal muscle cell, or a cardiomyocyte.
82. The kit of claim 81, wherein the VEGF is VEGF1-165, whose amino acid sequence is represented by SEQ ID NO: 1.

83. A kit comprising a dose of a polynucleotide that encodes a vascular endothelial growth factor (VEGF), or that encodes a polypeptide comprising an active site of the VEGF, wherein the coding sequence is operably linked to an expression control sequence, the dose being sufficient to induce arteriogenesis, lymphangiogenesis, vasculogenesis, cardiomyogenesis, or mitosis or proliferation of a smooth muscle cell, a skeletal muscle cell, or a cardiomyocyte.
84. The kit of claim 83, wherein the dose is between about 0.003 and about 0.36 nmoles /kg.
85. The kit of claim 84, wherein the dose is between about 0.01 and about 0.10 nmoles/kg.
86. The kit of claim 83, wherein the polynucleotide is inserted in a plasmid vector and is pUVEK15VEGF, and the concentration of the pUVEK15VEGF is between about 0.5 and about 4 ng/mL.
87. A method for inducing arteriogenesis, lymphangiogenesis, vasculogenesis, or cardiomyogenesis, comprising administering to a cell or tissue in need thereof a dose of a VEGF polypeptide, or a polypeptide comprising an active site of the VEGF, the dose being sufficient to induce arteriogenesis, lymphangiogenesis, vasculogenesis, or cardiomyogenesis.
88. The method of claim 87, wherein the VEGF is VEGF1-165, whose amino acid sequence is represented by SEQ ID NO: 1.
89. The method of claim 87, which is carried out in vivo, and wherein a sufficient dose of the polypeptide is administered to a subject in need of such treatment to induce arteriogenesis, lymphangiogenesis, vasculogenesis, or cardiomyogenesis.
90. A method for inducing mitosis or proliferation of a cardiomyocyte, comprising administering to the cell a sufficient dose of a VEGF polypeptide, or a polypeptide that comprises an active site of the VEGF, to induce the mitosis or proliferation.
91. The method of claim 90, wherein the VEGF is VEGF1-165, whose amino acid sequence is represented by SEQ ID NO: 1.
92. The method of claim 90, which is a method of tissue regeneration.
93. A kit comprising
- (a) a VEGF polypeptide, or a polypeptide the comprises an active site of the VEGF, and

(b) a label or instructions indicating a use for the polypeptide to induce arteriogenesis, lymphangiogenesis, vasculogenesis, or cardiomyogenesis, or mitosis or proliferation of a cardiomyocyte.

94. The kit of claim 93, wherein the VEGF is VEGF1-165, whose amino acid
5 sequence is represented by SEQ ID NO: 1.

95. The method of claim 87, wherein the polypeptide is administered in a single dose of between about 0.35 and about 3.5 mg/kg, wherein the mgrams are of an active VEGF polypeptide.

96. The method of claim 90, wherein the polypeptide is administered in a single dose
10 of between about 0.4 and about 1.4 mg/kg, wherein the mgrams are of an active VEGF polypeptide.

97. The method of claim 90, wherein the VEGF polypeptide is modified such that it exhibits enhanced bioavailability, biological activity, or half-life, and/or wherein the VEGF is formulated in a slow-release formulation.

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